



Pediatric Focused Safety Review: Abilify[®] (aripiprazole)

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Amy M. Taylor, MD, MHS

**Pediatric and Maternal Health Staff
Office of New Drugs**

**Center for Drug Evaluation and Research
Food and Drug Administration**



Outline

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- PREA Studies
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Background Drug Information

Abilify® (aripiprazole)

- **Drug:** Abilify® (aripiprazole)
- **Formulations:** oral tablets, oral disintegrating tablets, oral solution, immediate release injectable (intramuscular)
- **Therapeutic Category:** Antipsychotic (atypical)
- **Sponsor:** Otsuka Pharmaceutical and Bristol-Myers Squibb



Background Drug Information

Abilify® (aripiprazole)

Indications:

Oral formulations

- Treatment of irritability associated with autistic disorder: studies in patients aged 6 to 17 years
- Treatment of schizophrenia: studies in patients aged 13 years and older
- Acute treatment of manic or mixed episodes associated with bipolar I disorders as monotherapy and as an adjunct to lithium or valproate: studies in patients aged 10 years and older
- Maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate: studies in adults
- Adjunctive treatment of major depressive disorder: studies in adults

Injectable formulation

- Acute treatment of agitation associated with schizophrenia or bipolar disorder: studies in adults



Background Drug Information continue Abilify® (aripiprazole)

- **Original Market approval:** November 15, 2002
- **Pediatric Exclusivity Granted:** November 14, 2007
- **PREA labeling changes related to this presentation:** November 19, 2009



PREA Pediatric Studies Abilify® (aripiprazole)

- Two 8-week placebo-controlled trials in pediatric patients (6 to 17 years) with autistic disorder and demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination.
 - Primary endpoint: change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I).
 - Note: Clinical Global Impression-Improvement (CGI-I) scale also used for assessment



PREA Pediatric Studies

Abilify® (aripiprazole)

Efficacy results:

- First study (n=98) – significantly improved scores on the ABC-I subscale and CGI-I scale compared with placebo. Mean daily dose 8.6 mg/day
- Second study (n=218) – significantly improved scores on the ABC-I subscale compared with placebo at all dose levels (5 mg/kg, 10 mg/kg, and 15 mg/kg)



PREA Pediatric Studies

Abilify® (aripiprazole)

Safety results:

Commonly observed adverse reactions in short-term, placebo-controlled trials of pediatric patients (6-17 years) with Autistic Disorder treated with oral Abilify®

Preferred Term	Percentage of Patients Reporting Reaction	
	Aripiprazole (n=212)	Placebo (n=101)
Sedation	21	4
Fatigue	17	2
Vomiting	14	7
Somnolence	10	4
Tremor	10	0
Pyrexia	9	1
Drooling	9	0
Decreased Appetite	7	2
Salivary Hypersecretion	6	1
Extrapyramidal Disorder	6	0
Lethargy	5	0



PREA Pediatric Labeling Changes Abilify® (aripiprazole)

- 2 Dosage and Administration: 2.4 dosing for irritability associated with autistic disorder
- 6 Adverse Reactions: 6.2 Adverse reactions seen in clinical trials in autistic disorder described including dose –related adverse reactions, extrapyramidal symptoms, and weight gain
- 14 Clinical Studies: 14.4 Clinical studies in autistic disorder are described.



Relevant Safety Labeling Abilify® (aripiprazole)

Boxed Warning related to pediatrics:

Children, adolescents and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders are at increased risk of suicidal thinking and behavior



Relevant Safety Labeling Abilify® (aripiprazole)

Warnings and precautions related to pediatrics:

- *Suicidality and Antidepressants*: Increased risk of suicidality in children, adolescents, and adults with major depressive disorders (5.2)
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia*: Discontinue if clinically appropriate (5.4)
- *Hyperglycemia and Diabetes Mellitus*: Monitor glucose regularly in patients with and at risk for diabetes (5.5)



Relevant Safety Labeling Abilify® (aripiprazole)

Warnings and precautions related to pediatrics (continued):

- *Orthostatic Hypotension:* Use with caution in patients with known cardiovascular or cerebrovascular disease (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis:* have been reported with antipsychotics including ABILIFY. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.7)



Relevant Safety Labeling Abilify® (aripiprazole)

Warnings and precautions related to pediatrics
(continued):

- *Seizures/Convulsions:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.8)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery (5.9)
- *Body Temperature Regulation:* Disruption of the body's ability to reduce core body temperature (5.10)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk patients (5.11)



Abilify[®] (aripiprazole) Drug Use U.S. Outpatient Retail Setting (November 2009 – March 2011)¹

- **Total population:** 9.7 million prescriptions and 1.9 million patients were dispensed prescriptions for aripiprazole, cumulative
- **Pediatric population:** 1.9 million prescriptions and 369,000 patients were for patients 0 to 17 years old
 - 11% prescriptions for 13 to 17 year olds
 - 8% prescriptions for 7 to 12 year olds
 - 1% prescriptions for 3 to 6 year olds

¹SDI, Vector One®: National and Total Patient Tracker, November 2009-March 2011. Data Extracted July 2011.



Abilify[®] (aripiprazole) Drug Use Prescribing Specialty and Diagnoses (November 2009 – March 2011)¹

- Top prescribing specialty for aripiprazole prescriptions was Psychiatry (62%)
- Pediatricians accounted for 2% of aripiprazole prescriptions
- Top diagnoses code in pediatric patients:
 - Patients aged 3-6 years and 13-17 years: “Bipolar Disorder”(ICD-9 code 296.7)
 - Patients aged 7-12 years: “Affective Disorder” (ICD-9 code 296.9)

¹SDI, Vector One®: National and Physician Drug and Diagnosis with Pain Panel. November 2009-March 2011. Data Extracted July 2011.



Previous PAC Safety Reviews Abilify® (aripiprazole)

December 8, 2009

Safety review of Abilify®

- Committee recommended additional information on weight gain be added to labeling
- Committee discussed concerns about use of the atypical antipsychotics for ADHD
- Committee requested FDA review use data associated with a diagnosis of ADHD without other co-existing diagnoses



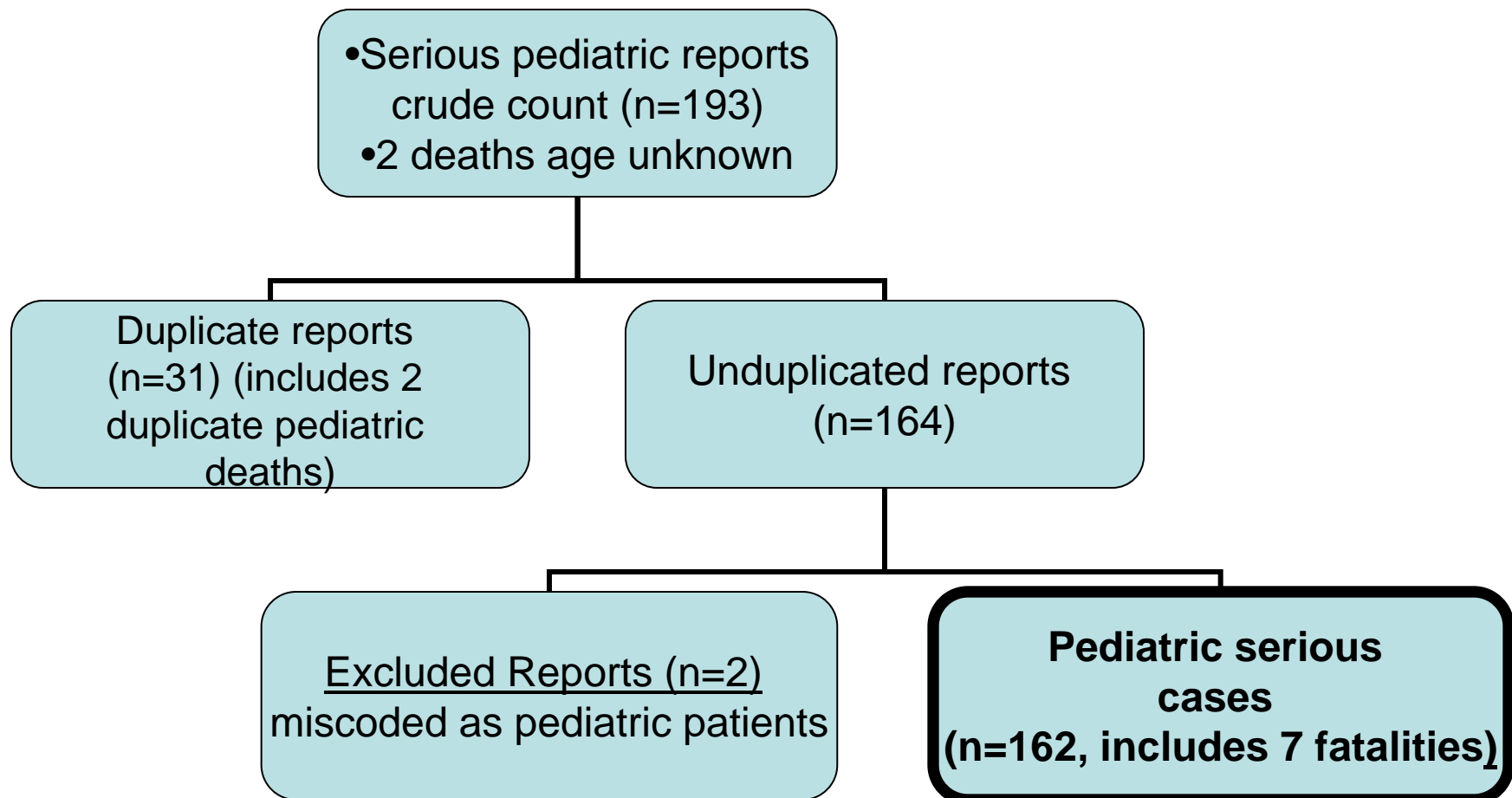
Crude Counts* of Abilify® Adverse Event Reports from May 1, 2009 to May 1, 2011

	All reports (US)	Serious**(US)	Death (US)
Adults (≥ 17 yrs.)	2666 (1769)	1664 (778)	183 (96)
Pediatrics (0-16 yrs.)	438 (374)	193 (131)	7 (3)
Unknown Age (Null values)	1495 (1353)	399 (264)	25 (17)
All Ages	4599 (3496)	2256 (1173)	215 (116)

*May include duplicates

**Serious adverse drug experiences per regulatory definition (CFR 3414.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

Pediatric Case Selection





Characteristics of Serious Pediatric Cases aripiprazole (n=162)

- Gender
 - Male (n=98)
 - Female (n=53)
- Age
 - 0<1 month (n=15)
 - 1 month - < 2 years (n=11)
 - 2 – 5 years (n=6)
 - 6-11 years (n=54)
 - 12 – 16 years (n=76)



Characteristics of Serious Pediatric Cases aripiprazole (n=162)

- Dosing (n=65)
 - Mean: 13.2 mg; Median: 10 mg
 - Range: 2 mg to 70 mg
- Duration of therapy (n=46)
 - Mean: 238 days; Median: 47.5 days
 - Range: 1 day to 8 years



Pediatric Deaths (n=7) Abilify® (aripiprazole)

- 10 year old male died of multiple organ system failure due to or as a consequence of ischemic cardiomyopathy, coronary artery stenosis and congenital heart disease. He was on aripiprazole for 2 years, but discontinued the drug one month prior to his death.
- 13 year old male with bipolar disorder had a seizure while on aripiprazole therapy for about a week. The patient died after an unspecified period of time. The cause of death was not reported.



Pediatric Deaths continued (n=7)

Abilify® (aripiprazole)

- 14 year old male died with symptoms of possible abscessed wisdom teeth consisting of headache, tooth and jaw pain, and possible fever. Patient was on aripiprazole, lisdexamfetamine, quetiapine, sertraline, valproic acid, clonidine, diphenhydramine, meloxicam APAP with codeine and penicillin. The autopsy report indicated an elevated tryptase level, but stated “can’t rule-in or rule-out anaphylaxis”.



Pediatric Deaths continued (n=7)

Abilify® (aripiprazole)

Premature neonates:

- Premature neonate born with Tetralogy of Fallot, facial dysmorphism, and multiple other malformations after exposure to aripiprazole throughout entire pregnancy. Six days after birth, he died due to Tetralogy of Fallot, hemothorax and hemopericardium post operatively. Mother had chromosomal microdeletion 22 with Tetralogy of Fallot.
- Premature twins delivered following exposure to aripiprazole throughout entire pregnancy. The male neonate died at 2 days of life. The female neonate died one week after delivery. The case is confounded by preterm delivery of a twin pregnancy.



Pediatric Deaths continued (n=7)

Abilify® (aripiprazole)

Premature neonates (continued):

- A premature male neonate died one day after delivery, following exposure to aripiprazole for “almost the entire first trimester”. The was also exposed to escitalopram, lorazepam (discontinued early in the pregnancy) and zolpidem. The mother had a history of Hepatitis B and experienced chorioamnionitis and premature rupture of the membranes, leading to the neonate’s death.



Pediatric Serious Non-Fatal Adverse Events Abilify® (aripiprazole) (n=155)

- Extrapyramidal symptoms (n=27)
- Motor disturbances (n=2)
- Metabolic adverse events (n=16)
- In-utero exposure (n=20)
- Accidental exposure (n=7)
- Lethargy and somnolence (n=2)
- Other serious miscellaneous events (n=81)



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Extrapyramidal symptoms (n=27)

- Dystonia (n=17) – acute (n=9), tardive (n=5), and no time to onset reported (n=3)
- Parkinsonism (n=7)
- Tardive dyskinesia-like symptoms (n=2)
- Unspecified EPS (n=1)

Motor Disturbances (n=2)

- Facial paralysis and akathisia
- Speech impairment and “major swelling of the whole body”



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Metabolic Adverse Events (n=16)

- Weight gain (n=9)

Weight changes reported in the AERS pediatric case series for aripiprazole, organized by age in years		
Age in Years	Daily Dose	Amount of Weight Gained
7	30 mg	
7		54.8 lbs. in two years
9		17 lbs. over an unspecified period of time
10	5 mg	
10	5 mg	Approximately 15 lbs. in 2.5 wks (78 lbs to 93 lbs)
10	6 mg	Over 20 lbs. in three months
13	10 mg	10 lbs. in two weeks
15	15 mg	33 lbs. in seven months
16		Greater than 50 lbs. over approximately two years

The blank fields in the table represent information omitted from the AERS report by the reporter.



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Metabolic Adverse Events (continued)

- Diabetes Mellitus (n=3)
- Metabolic Changes (n=3)
 - Central obesity, dyslipidemia, hypertension, hyperglycemia, and metabolic syndrome
- Glucose Abnormality (n=1)



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

In-Utero Exposure (n=20)

- Congenital anomaly (n=9)
 - Cerebral palsy, Down's syndrome, congenital heart defects (n=3), accessory mamilla, plagiocephaly, tracheoesophageal fistula, fetal growth restriction, cryptorchism
- Miscellaneous (n=11)
 - Prematurity (3), small for dates (3), fetal distress syndrome (2), benign neonatal sleep myoclonus (1), fetal heart rate decreased (1) and neonatal asphyxia(1)



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Accidental exposure (n=7)

Lethargy and Somnolence (n=2)



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Miscellaneous Events (n=81)

- Psychiatric (n=25) – abnormal behavior, aggression, anger, emotional disorder, hallucinations, mania, panic, psychotic disorder/behavior, suicide attempt, suicidal ideation, tic (history of Tourette syndrome), worsening of Tourette syndrome, withdrawal syndrome



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Miscellaneous Events (continued):

- Nervous system (n=20) – convulsions (17), migraine headache, sleep apnea, neuroleptic malignant syndrome
- Gastrointestinal (n=4) – celiac disease aggravation, esophageal muscle spasm, tooth loss, abdominal pain, increased blood uric acid



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Miscellaneous Events (continued):

- Hepatobiliary (n=4) – hepatic fibrosis, hepatic failure (concomitant lamotrigine is labeled for hepatic failure), hepatic steatosis (history of obesity), hepatic steatosis with weight decreased
- Cardiac (n=3) – bundle branch block, cardiac arrest, cardiac disorder, chest pain, irregular heart rate



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Miscellaneous Events (continued):

- Blood and lymphatic system (n=3) – agranulocytosis, decreased white blood cells, decreased platelets, decreased hemoglobin, idiopathic thrombocytopenic purpura
- Investigations (n=3) – increased alanine aminotransferase, increased aspartate aminotransferase, electrocardiogram change, QT prolongation



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Miscellaneous Events (continued):

- Eye (n=3) – cataract, corneal disorder, corneal edema, visual acuity reduced
- General (n=2) – hyperhidrosis, hot flush, chills
- Renal and urinary (n=2) – acute renal failure, urinary incontinence
- Skin and subcutaneous tissue (n=2) – drug rash with eosinophilia and systemic symptoms and rhabdomyolysis, rash



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Miscellaneous Events (continued):

- Vascular (n=2) – cerebral venous thrombosis,
hypertensive crisis
- Musculoskeletal and connective tissue (n=1) – muscular weakness
- Neoplasms benign, malignant and unspecified (n=1) – brain neoplasm with cerebrovascular accident
- Endocrine (n=1) – hypothyroidism



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Miscellaneous Events (continued):

- Infections and infestations (n=1) – infection
- Injury, poisoning and procedural complications (n=1) – overdose
- Immune system (n=1) – angioedema
- Reproductive system (n=1) – priapism



Pediatric Serious Non-Fatal Adverse Events continued (n=155) Abilify® (aripiprazole)

Miscellaneous Events (continued):

- Multiple diagnoses (n=1) – amnesia, dysarthria, glossodynia, auditory hallucination, muscle twitching, swollen tongue, visual impairment



Summary Pediatric Focused Safety Review

Abilify® (aripiprazole)

- This concludes the pediatric focused safety review
- No new safety signals identified
- FDA is and will be reviewing additional data regarding pediatric metabolic adverse events related to the use of atypical antipsychotics
- FDA recommends continuing routine, ongoing post-marketing safety monitoring
- Does the Committee concur?



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Tracy Salaam, PharmD
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Laura Governale, PharmD, MBA
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